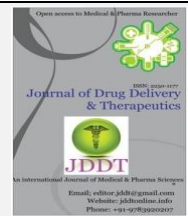


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Review Article

Plasmapheresis in Management of Oral Autoimmune Disorders

Dr Kanupriya Gupta

MDS- Oral Pathology, Ph.D Research Scholar & Senior Research Fellow, Division of Oral Pathology, Faculty of Dental Sciences, IMS, BHU, Varanasi, India

ABSTRACT

Systemic autoimmune diseases based on an immune pathogenesis produce autoantibodies and circulating immune complexes, which cause inflammation in the tissues of various organs. In most cases, these diseases have a bad prognosis without treatment. Autoimmune disorders are a group of poorly understood diseases in which the body fails to distinguish between self and non-self which could result in damage to the self. Oral mucous membrane may be affected by a variety of autoimmune mucocutaneous diseases such as pemphigus, bullous pemphigoid, mucous membrane pemphigoid, lichen planus, erythema multiforme, Steven Johnson syndrome, epidermolysis bullosa, linear IgA disease etc. These diseases (commonest being pemphigus) cannot be controlled in some cases, even with very high doses of systemic corticosteroids and immunosuppressive agents. In such cases plasmapheresis is one of the most effective therapeutic methods to deplete sera of immunoglobulin, including pathogenic autoantibodies. The aim of this review is to describe plasmapheresis as an adjunct therapy for oral autoimmune disorders.

Keywords: autoimmune diseases, plasmapheresis, pemphigus, lichen planus, erythema multiforme, Steven Johnson syndrome, epidermolysis bullosa, linear IgA disease

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*Address for Correspondence:

Dr Kanupriya Gupta, MDS- Oral Pathology, PhD Research Scholar & Senior Research Fellow, Division of Oral Pathology, Faculty of Dental Sciences, IMS, BHU, Varanasi- 221005, India

INTRODUCTION

Autoimmune disease occurs when an adaptive immune response is triggered inappropriately against self-antigens, antigen cannot be cleared by normal immune processes resulting in a sustained immune response, chronic inflammation and injury to involved tissues. Oral mucocutaneous disease can be divided into two groups intraepithelial and sub epithelial ulcerations. Various treatment modalities of these disorders utilize systemic steroids or immunosuppressive agents. While effective these treatments are limited by serious side effects and/or lag time before they become effective. Recently, plasmapheresis has been used successfully in treating several diseases believed to be caused by circulating antibodies.

Plasmapheresis is derived from a Greek word meaning to take away by force. The term was first used by Abel in 1914 in his report entitled, "Plasma removal with return of corpuscles (plasmapheresis)" wherein he reported that large amounts of plasma could be collected from an animal if the red blood cells were returned¹. Plasmapheresis is a procedure that involves separating the blood, exchanging the plasma (typically

with donor plasma or albumin solution), and returning the other components, primarily red blood cells, to the patient. Although discovered in 1914, the concept of plasmapheresis was first tried therapeutically in man in the year 1959. Michael Rubinstein was the first person to use plasmapheresis to treat an immune-related disorder when he saved the life of an adolescent boy with thrombotic thrombocytopenic purpura (TTP) at the old Cedars of Lebanon Hospital in Los Angeles².

Role of plasmapheresis in autoimmune diseases
Therapeutic benefit of plasmapheresis is believed to result from the removal of potential pathologic substances, which may include auto antibodies, circulating immune complexes, cytokines, or toxins^{3,4}. Other factors, which may have a therapeutic role, include enhanced clearance by the reticuloendothelial system in immune complex-mediated diseases^{5,6}, stimulation of lymphocyte clones enhancing the effect of cytotoxic therapy^{7,8}, and replenishing a missing factor by plasma infusion^{9,10}.

Difficulties encountered while performing plasmapheresis may trigger increase in antibodies which partially

replace and sometime exceed or overshoot plasmapheresis level. Two different processes are involved in this rebound ^{11,12}.

The first process is minor and peaks rapidly in 24 to 48 hours. It is due to Passive diffusion of extracellular immunoglobulin back into the circulation. It replaces about half of the IgG and perhaps 20% of the IgM that has been removed. This rebound cannot be altered because it is a physical phenomenon. It cannot cause an overshoot in serum antibody levels and it can be overcome by repeated plasmapheresis. A practical implication of this mechanism is that it is best to space plasmapheresis two days apart to allow full re-equilibration of antibody levels between procedures.

The second process is a feedback mechanism that regulates the serum level of specific antibodies. Depletion of serum antibodies as induced by plasmapheresis stimulates a burst of new antibody synthesis that replaces and usually overshoots that which has been removed. This feedback mechanism was first describe in animals and then documented in humans ^{13,14}. The effect of this mechanism on plasma antibody levels is slower at onset but much greater in magnitude. Antibody levels peaks one to two weeks following plasmapheresis and at that point can be substantially above pre-depletion levels. This rebound, which results from new antibody synthesis, can be blocked by preventing B cell synthesis^{12,15}.

Thus the ability of plasmapheresis to reduce antibody levels will depend on the balance between the rate of new antibody synthesis and volume and frequency of plasma removal. To shift the balance in a favourable direction, it is critical to perform plasmapheresis intensively and to suppress new antibody synthesis.

The rebound in antibody levels triggered by antibody depletion can be suppressed in animals by Cyclophosphamide¹² and more effectively by combination therapy with Cyclophosphamide and Cytosine arabinoside¹⁵. Many authors have successfully used Cyclophosphamide or Azathioprine in doses of 100 to 150 mg/day in humans. Small doses of these drugs should not be used as they can selectively inactivate suppressor¹⁶ cells and enhance established antibody response to antigen¹⁷. The rebound may also be suppressed by high doses of Prednisolone.

Recommendations for performing plasmapheresis

It is advisable to perform plasmapheresis three times per week removing 1.8 to 2 litres of plasma per procedure and adding one unit of gamma globulin to the replacement fluid at the end of each procedure to maintain normal levels of immunoglobulin. Azathioprine or cyclophosphamide at a dose of 50mg twice a day to three times a day is used to minimize rebound in antibody levels. Corticosteroid dose can be left unchanged¹⁸.

Applications of plasmapheresis in various oral autoimmune mucocutaneous disorders:

Plasmapheresis has been successfully tried as an effective therapeutic modality in:

1. Pemphigus vulgaris
2. Pemphigus foliaceus
3. Bullous pemphigoid

4. Cicatricial pemphigoid
5. Erythema multiforme
6. Dermatitis herpetiformis
7. Toxic epidermolysis bullosa
8. Linear IgA disease
9. Paraneoplastic pemphigus

Contraindications

1. Patients who cannot tolerate central line placement.
2. Patients who are actively septic or are hemodynamically unstable.
3. Patients who have allergies to fresh frozen plasma or albumin depending on the type of plasma exchange.
4. Patients with heparin allergies should not receive heparin as an anticoagulant during plasmapheresis.
5. Patients with hypocalcemia are at risk for worsening of their condition because citrate is commonly used to prevent clotting and can potentiate hypocalcemia.

COMPLICATIONS

Plasmapheresis procedures are relatively safe; the overall incidence of adverse effects, which are mostly reversible, is about 4.75%. Notable side effects include transfusion reaction, urticarial reaction, and citrate-related nausea and vomiting, mostly in patients receiving donor plasma. Vasovagal or hypotensive reactions are more common in neurologic patients than in hematologic and rheumatologic patients. Death is rare and is usually related to the underlying disease¹⁹.

CONCLUSION

Plasmapheresis is a valuable treatment in patients with autoimmune diseases in which all other treatment modalities have failed. Hence it can be employed as a treatment of choice in certain autoimmune diseases involving the oral cavity in which the adverse effects of other treatment modalities outweigh the therapeutic effects.

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